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Review

Adaptive and maladaptive psychobiological responses to severe psychological stress: implications for the discovery of novel pharmacotherapy

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Abstract

Post-traumatic stress disorder (PTSD) is one of the few DSM-IV diagnoses contingent upon a psychosocial stressor. In this context, there is an urgent need to acquire a better understanding of both the adaptive and maladaptive psychobiological responses to traumatic stress. Preclinical investigators have utilized a variety of animal models to identify the behavioral and neurobiological features of the organism's response to stress. However, given the complexity of the healthy and pathological human response to physiological and psychological stress, the extent to which the animal data is immediately transferable to human remains to be fully determined. This review draws upon preclinical and clinical literature to examine the transformation of an adaptive human stress response into a maladaptive and debilitating mental disorder. An integrative psychobiological model for PTSD is presented, linking psychological processes and behavioral patterns with current findings in neurocircuitry, neurochemistry and psychophysiology. The implications of this model for the discovery of novel pharmacological approaches to the treatment of severe psychological distress are discussed.

Keywords: Post-traumatic stress disorder; Adaptive and maladaptive; Fear and anxiety; Fear conditioning; Extinction; Learned helplessness; Neural circuitry; Neurochemistry; Psychophysiology; Pharmacotherapy

Contents

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Stress is an often used and very broad term, applied to external and internal stimuli that may alter the physical and mental homeostasis of a person or an animal [1]. Interestingly, and contrary to initial emphasis upon physical stressors [2], psychological and experiential factors are among the most powerful of stressors: e.g. novelty, withholding of reward, and anticipation of punishment (rather than the punishment itself) are among the most potent activators of physiological stress systems [3]. Psychometric data collected at the acute aftermath of exposure to traumatic events reveal high levels of distress in the majority of subjects, consisting of preoccupation with and re-experiencing the outstanding event, fear, anxiety and arousal, sleep difficulties, emotional numbness and withdrawal or dysphoric and irritable mood and loss of the sense of basic safety [4–6]. Yet, despite the severe initial emotional response, most people who undergo a traumatic event will not develop post-traumatic stress disorder (PTSD) [7,8]. In fact, it is currently impossible to predict prognosis based upon behavioral response in the first days following trauma. Most individuals employ innate coping strategies that eventually serve to alleviate distress, regain sense of well being and avoid chronification into PTSD.

Symptoms of PTSD are largely similar to those observed soon after trauma. They are phenomenologically divided into three clusters: intrusive recollections, avoidant behavior and increased arousal. Of these three clusters, intrusive recollections and increased arousal generally appear very soon after trauma, while avoidance may appear later and its presence often determines diagnosis of PTSD [9]. In this review we present a comprehensive psychobiological model of the evolution of PTSD. An emphasis is placed on the neurocircuitry, neuroendocrinology and neurochemistry mediating this process. Our presentation follows DSM-IV classification of PTSD, and illustrates, within each cluster, how initially protective and adaptive mechanisms evolve into maladaptive responses that further increase vulnerability to this disorder. Since much of this model is based upon preclinical research, most, but not all, PTSD symptoms are addressed.

1. Reexperiencing

Reexperiencing may involve thoughts, memories, perceptions, images or dreams. The traumatic event persistently intrudes into awareness, triggered by external or internal, often unremarkable, stimuli. The emotional response is highly stressful. Patients may act or feel as if they are actually reliving the traumatic experience and in severe cases may even lose orientation to time and place (i.e. dissociate). Given the association between traumatic recall and seemingly unrelated stimuli and the ensuing fearful response, the mechanism of fear conditioning has often been suggested as a model for the reexperiencing phenomena in PTSD [10–14].

Conditioned fear responses have been studied mostly in rodents. If a non-threatening stimulus (e.g. tone, termed conditioned stimulus (CS)) is presented together with an aversive stimulus (e.g. shock, termed unconditioned stimulus (US)), an animal soon exhibits a fear response (termed conditioned response, (CR)) to the presentation of the CS alone. A CR is also evoked when the animal is placed in the environment (e.g. cage) in which the experiment took place. These two aspects of fear conditioning are termed ‘explicit cue’ and ‘context’ conditioning. Fear conditioning may be very rapidly acquired [11], often with single exposure to a pairing of CS–US sufficing to induce a conditioned response to previously neutral stimuli [10], and may also be very persistent, with the CS–CR coupling remaining potentially active indefinitely [10,11,15]. When presentation of a CS followed by a US (termed CS +) is alternated with presentation a different neutral CS that is not followed by a US (termed CS −), the latter CS is understood as a safety signal. This sequence of stimuli presentation is termed ‘differential fear conditioning’. After conditioning is acquired, repeated presentation of the CS without a US (non-reinforcement) is termed extinction, a process in which the CR is reduced. In contrast with earlier theories, the reduction in fear that follows extinction does not result from forgetting or memory erasure [16]. Rather, it involves the formation of new non-aversive associations that ‘compete’ with the prior fear-conditioned associations [17]. The aversive conditioned association is not erased, and may be reactivated at particular circumstances after extinction. Examples of such reactivated conditioning are the renewal of a CR if an extinguished CS is presented in a context different from the one in which extinction was performed or the reinstatement of fear conditioning upon pairing of the CS with a US [17].

Fear conditioning is a highly adaptive mechanism in life-threatening circumstances [18,19], optimizing response to hazard, ensuring vigilance to potential danger and preventing diffusion of attention to meaningless stimuli [20]. For example, the conditioned fear responses to predator smell

in an animal or to the shriek of a bomb in soldiers at war clearly demonstrate survival benefit. The occurrence of fear conditioning phenomena across species [21] supports an evolutionary role for this mechanism. In contrast, conditioned responses in PTSD are maladaptive and bring about fear and apprehension. The traumatic event is reexperienced in response to diverse trauma related, non-trauma related and probably also internal, ill defined, stimuli. Patients with PTSD are impaired in their ability to discriminate between threat-related and non-related stimuli. This has been experimentally demonstrated by studies using differential fear conditioning. In healthy subjects, levels of anxiety following CS − are much lower than those following CS + . In contrast, patients with PTSD show increased skin conductance response to CS − [22] and lack a differential response to CS regardless of whether they are followed by an US [23].

We propose that reexperiencing symptoms in PTSD result from implementation of impaired and maladaptive fear conditioning-like mechanisms in response to severe stress. Maladaptive acquisition of reexperiencing symptoms is enhanced by non-associative learning processes and is further facilitated by learned helplessness behavior.

Several, potentially complementary mechanisms may explain the transition of adaptive fear conditioning into uncontrollable (and intrusive) reexperiencing in PTSD (Fig. 1 and Table 1): (a) emotional-fear memories are more vividly encoded and more amenable to recall; (b) the unconditioned response (UR) is maintained even in the absence of a US; (c) the capacity to integrate context and content related information into one coherent stimulus is absent; (d) conditioned response to generalized stimuli is not diminished; (e) extinction is absent despite stimulus non-reinforcement; (f) fear conditioning is enhanced following exposure to inescapable stress and resultant learned helplessness behavior.

(a) A large body of evidence suggests that arousing, fearful or emotionally exciting events are remembered better and for longer periods of time than emotionally neutral events [24]. In a landmark study, Cahill et al. [25] showed that administration of the beta-adrenergic blocker propranolol impaired memory for an emotional narrative but had no effect on memory for an emotionally neutral story. Since traumatic events stimulate the release of cortisol, corticotropin releasing hormone (CRH), epinephrine (E) and norepinephrine (NE), it has been hypothesized that these neurotransmitters enhance consolidation of emotional memory [26,27]. Animal data has also shown that administration of CRH, cortisol, E and NE enhance both consolidation of memory at or around the time of training and memory retrieval when administered at the time of memory testing [28,29]. Increased peritraumatic hormonal or catecholaminergic secretion and/or increased receptor sensitivity in vulnerable individuals may lead to augmented emotional memory storage or enhanced retrieval and evolution of PTSD.

Reexperiencing accesses emotional memory. Short, and even fully consolidated long-term memories (LTM) become unstable upon reactivation [30]. Therefore, reactivated memories require another round of consolidation to return to memory storage, a process referred to as reconsolidation [31]. Clearly, memory reactivation is very common in PTSD. In an animal study examining consolidation and reconsolidation of an emotional task [32], memory-impairing effects of the beta-blocker propranolol were greater when the drug was administered after a reactivation trial than when administered immediately after the initial training. This suggests that ongoing distress, accompanied by catecholamine and cortisol secretion, may enhance reconsolidation of emotional memories in PTSD. In contrast, it also suggests that psychotherapeutic or psychopharmacologic interventions performed even late during the course of PTSD may well be beneficial.

(b) Although the US is absent, CS triggered reexperiencing in PTSD often evokes an emotional response very similar to the one evoked by the US, i.e. an unconditioned response (UR). This response is reminiscent of Eyesenck's theory of incubation [33], which postulates that in select cases where there is an overlap between CR and UR, repeated presentation of the CS in the absence of the US may perpetuate fear conditioning rather than promote extinction. The UR is brought about by emotional and mental representations of the traumatic event(s) (i.e. the US), triggered by a CS. This capacity for vivid mental imagery and representation may be unique to humans, partly explaining resistance to extinction in PTSD (see below; for other anxiety disorders, see Ref. [34]) rarely seen in lower order animals such as rodents.

Repeated CS triggered reexperiencing may also be conceived as a process of 'priming' whereby an augmented emotional response occurs after repeated provocation by the same stimulus [35]. This may reflect alleviation of amygdala inhibition and will be discussed below.

(c) Adaptive fear conditioning enables the individual to distinguish between safe and threatening stimuli and respond accordingly. The correct identification of safe and unsafe stimuli depends on proper integration of content and context information and serves a highly adaptive purpose. For example, trained soldiers will respond differently to a loud sound on the battlefield or when home on leave. Thus, response to CS (as well as to US) is context sensitive, as demonstrated in animals by the use of context modulation and occasion setting paradigms [36]. The intense fear response of patients with PTSD to CS regardless of context suggests impairment in their capacity to integrate context and content stimuli, illustrating how fear conditioning completely loses its adaptive function.

(d) Partial modification of the CS (i.e. generalization) has been shown in fear-conditioned animals to elicit a reduced CR [37]. Subsequent alterations of the novel CS elicit an even more moderate CR, soon reaching its complete annulment. This process may be viewed as serving to

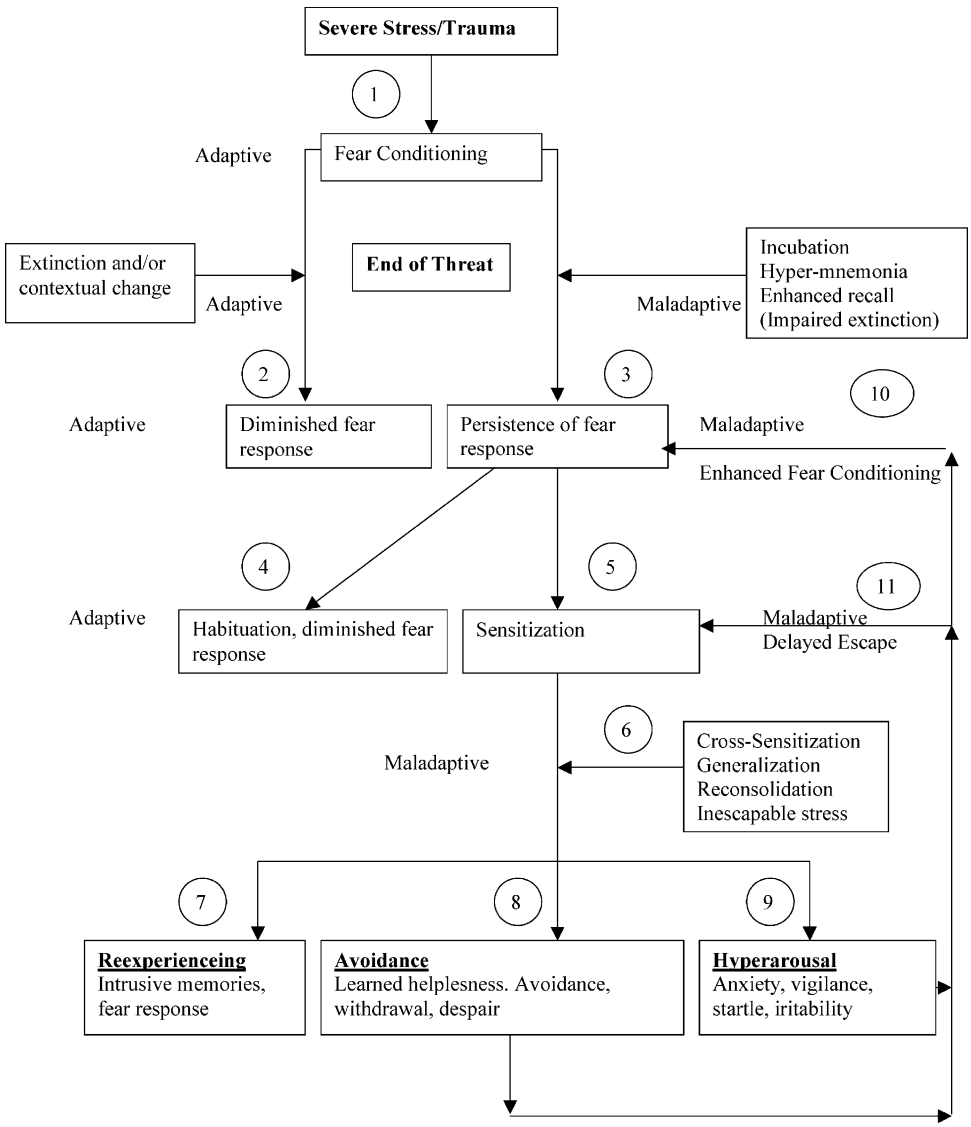

Fig. 1. Adaptive and pathological responses to a severe stressor. Exposure to a severe traumatic event (1) results in fear conditioning that serves an adaptive purpose as long as threat is present. After termination of danger, fear response is normally reduced (extinguished and/or diminished due to a contextual change, i.e. soldier returning from Iraq) (2). However, sometimes fear response persists despite termination of threat, even after a person has been removed from the threatening context (3). Hypothesized mechanisms that promote maladaptive fear conditioning are incubation, hyper-mnemonia and enhanced recall, deficit in integration of context and content and impaired alternative learning (see text for details). Fear response may then habituate and lose its aversive properties (4), or maintain and even augment them (5). Fear response often generalizes, and is evoked by stimuli only remotely related to the initial traumatic event, reflecting sensitization and cross sensitization of the neuronal system (6). All DSM-IV PTSD symptom clusters are observed at this stage: Reexperiencing (7), exhibiting a persistent, maladaptive and malfunctioning fear conditioning process, with a conditioned fear response to diverse, non-trauma related stimuli; Avoidance (8), where an avoidant and dysphoric behavioral response is observed similar to the animal model of 'learned helplessness'; and hyperarousal (9), reflecting incessant anxiety and absence of a safe haven, generalization and cross sensitization *of the* conditioned fear stimulus. Such non-associative learning processes increase baseline anxiety and result in full-blown fear responses, exacerbating the reexperiencing cluster. This cascade is positively reinforced by enhancement of fear conditioning (10) and delayed escape behavior (11) that are part of the learned helplessness syndrome.

maintain the adaptive capacity (specific recognition) of fear conditioning. In contrast, in PTSD generalization of the CS does not lead to a decrement in CR. Fear response is evoked by numerous and diverse stimuli, whose semblance to the traumatic event is not recognizable. Enhanced response to novel stimuli often occurs in individuals sensitized (i.e. repeatedly exposed, see below) to a different stimulus [38], and is termed 'cross sensitization'. Patients with PTSD are 'sensitized' by their repeated fear response to recurring CSs. Once a person is 'sensitized', even a non-conditioned and neutral novel stimulus may evoke an excessive response and become 'CS-like' within a fear conditioning paradigm. In this manner, 'generalization' of CS in patients with PTSD may represent synergism between associative and non-associative forms of learning.

(e) Persistent PTSD symptoms may also be viewed as a failure to extinguish the CR. As mentioned above, extinction is a process of alternative learning, rather than

Table 1
Neurobiological mechanisms and clinical symptom clusters in PTSD

Cluster	Clinical symptom	Psychophysiological model	Neurocircuitry	Neurochemistry	Impairment in PTSD
Reexperiencing	Intrusive recollections, thoughts, dreams; reexperiencing; intense psychological distress & fear	Maladaptive fear conditioning/ delayed extinction. Incubation. Increased reconsolidation. Impaired occasion setting	Amygdala, thalamus hippocampus, anterior cingulate and prefrontal cortex, locus coeruleus, primary somatosensory cortices, insula	Corticotropin releasing hormone (CRH), cortisol, mineralocorticoid receptor, glucocorticoid receptor, catecholamines, glutamate, gamma-aminobutyric acid (GABA)	Fear conditioning persists despite absence of threat. Extinction is delayed, due to intrinsic problem in this mechanism or due to hyper-mnemonic encoding and/or enhanced recall
Avoidance	Avoidance of intrapsychic or environmental recollections of trauma. Social withdrawal, detachment and diminished interest. Sense of foreshortened future	Inescapable stress – learned helplessness	Dorsal raphe nucleus, amygdala, thalamus, hippocampus, prefrontal cortex, nucleus accumbens, ventral tegmental area, peiaquaductal gray	Serotonin, dopamine, CRH, glutamate, GABA	Distressful, unavoidable, repeated intrusive recollections become an 'inescapable stressor', leading to a 'learned helplessness' like condition
Arousal	Anxiety, insomnia, lack of concentration, irritability, hyper-vigilance, startle	Delayed/absent habituation. Sensitization. Cross sensitization. Generalization	Locus coeruleus, bed nucleus stria terminalis, amygdala, hippocampus, nucleus accumbens, paraventricular hypothalamic nuclei, ventral tegmental area, periaquaductal gray	Norepinephrine, neuropeptide-Y, glutamate, GABA, cortisol, dehydroepiandrosterone, serotonin	Due to generalization and cross sensitization of threatening contextual stimuli, unsafe environment expands, all secure havens are abolished, leading to unremitting anxiety

one of forgetting. This means that the absence of CS reinforcement by a US will not in itself enable extinction unless accompanied by active learning. This capacity may be impaired in PTSD (possibly as a result of impaired glutamatergic *N*-methyl-D-aspartate (NMDA) neurotransmission, reviewed below).

The concept of extinction as a competitive learning process rather than memory erasure is also compatible with PTSD phenomenology: The foremost vulnerability factor for acquisition of PTSD is past history of trauma and childhood abuse [39,40]. Thus, re-exposure to a traumatic event (a US), even after extinction, could trigger PTSD, in accordance with the *reinstatement* construct. Such re-exposure could be particularly deleterious if occurring in a surrounding where the individual does not feel secure (i.e. *renewal*, as above). Likewise, this suggested mechanism of extinction may help explain the occurrence of 'delayed' PTSD, whereby patients who initially extinguished a post-traumatic fear response present with 'delayed' PTSD upon exposure to a particular cue or context. In addition, even 'asymptomatic' patients with (past) PTSD when faced with circumstances even remotely similar to their index trauma (witnessing MVA, assault, etc.) respond with an intense emotional reaction [41,42].

(f) Failure of the acute stress response to alleviate danger and fear causes the stress to be perceived as 'inescapable'. This experience is often accompanied by a behavioral pattern analogous with the animal model of 'learned helplessness'. Animal research has shown that fear conditioning is enhanced in this state, creating a vicious cycle of positive reinforcement between fear inescapable shock, learned helplessness and fear conditioning (explained in detail in Section 2)

1.1. Neural circuitry of re-experiencing and emotional memory

Neurocircuitry of fear conditioning and response has been well studied (Table 1). Upon exposure to a potentially threatening stimulus, information is transmitted by external and visceral sensory pathways to the thalamus. Afferents then reach the basolateral amygdala (BLA) via two parallel neural circuits: a rapid subcortical path ('short loop') directly from the dorsal ('sensory') thalamus, and a slower regulatory, cortical pathway ('long loop'), encompassing the primary somatosensory cortices, insula and anterior cingulate/prefrontal cortex. Response to the aversive stimulus is transmitted via the central nucleus of the amygdala (CE) midbrain, medulla and brain stem nuclei [43]. In addition, BLA afferents are densely connected to PFC and NAc. Pathways conveying the UCS have not been studied as much, but are believed to reach the BLA from the thalamus, parabrachial area, spinal cord and somatosensory cortical regions [10,44]. The immediate fear response is subjected to cortical processing and regulation, and may accordingly persist, change or end.

Integration of CS, UCS and resultant fear response are predominantly modulated by the amygdala [10,45], hippocampus[46], and bed nucleus of the stria terminalis [47] (BNST). The amygdala is implicated in encoding and consolidation of emotionally arousing events [26], such as those described in DSM-IV criterion A for PTSD. Lesions of the amygdala have been shown to block the enhancing effects of arousal of emotional memory encoding and consolidation. Lesions of the amygdala also block the memory-modulating effects of systemic administration of catecholeamines and cortisol [27]. Some controversy is as yet unresolved regarding the role of the hippocampus in fear conditioning (although it is clearly part of the neural circuitry of fear)—it may be crucial to stimulus processing and consolidation, or serve as no more than an input for sensory stimuli relay to the amygdala. It appears that the hippocampus has a crucial role in associating environmental stimuli and forming a coherent contextual representation of these stimuli [48]. Both pre [49] and post [50] training hippocampal lesions blocked consolidation of contextual fear memories. It has also been suggested that consolidation of contextual fear memory is a two stage process, with hippocampus serving for immediate memory consolidation and longer term storage undertaken by neocortical structures [18]. Thus, activation of nucleus accumbens (NAc) and anterior cingulate was observed during of fear-conditioned memories [51].

Less is currently known about neuroanatomy and mechanisms of extinction. Opinion differs regarding the roles of the medial prefrontal cortex [10,52,53] or amygdala [54–56] in this process. Extinction is considered a learned alternative to fear conditioning and as such undergoes STM and LTM storage and consolidation. It appears that the initial learning of extinction may be localized in the amygdala [57], while extinction recall selectively activates medial prefrontal neurons [58]. Lesions of mPFC dopamine (DA) neurons delay extinction of the conditioned fear stress response (with no effect on acquisition) indicating that prefrontal DA neurons are involved in facilitating extinction of the fear response. This suggests that reduced prefrontal cortical DA (or function) results in the preservation of fear [59].

Functional brain imaging studies in healthy subjects used conditioning paradigms to seek the neurocircuitry of fear and anxiety. FMRI studies have demonstrated activation of the amygdala during acquisition and extinction phases of conditioning [60]. In addition to the amygdala, fMRI studies show fear conditioning related activation in the anterior cingulate and precentral cortical regions [60,61]. PET studies of aversive conditioning in healthy subjects describe activation of additional cortical regions, such as anterior cingulate, precentral and premotor regions [62], and orbito-frontal, prefrontal and temporal cortices [63]. Functional brain imaging studies of PTSD utilized provocation of

traumatic memory to demonstrate amygdala and anterior cingulate involvement in PTSD. This activation of the pre-frontal cortex (PFC) is thought to represent modulation and/or inhibition of the expression of the fear response. Reduced PFC activation in PTSD is compatible with excessive and prolonged expression of fear response and absence of inhibitory processes [64]. Right amygdala activation was reported in combat related PTSD when patients and controls were exposed to traumatic imagery and combat pictures [65,66], while the left amygdala was activated in response to combat sounds [67]. Volumetric brain studies that focused on the hippocampus often reported non-significant decreased amygdala volume in patients with PTSD compared with healthy controls [68–72]. A recent study reported significantly smaller left amygdala volume in female cancer survivors with intrusive memories, compared to survivors without such memories [73]. Additional studies directed at the amygdala are required to determine this structure's morphometry in PTSD. The anterior cingulate has also been subjected to considerable imaging research. Compared with trauma exposed or healthy control subjects, PET studies generally show decreased perfusion in the anterior cingulate in patients with PTSD after traumatic memory provocation [64,74,75]. Recent fMRI studies similarly show reduced perfusion in anterior cingulate in patients with PTSD compared to controls after mental imagery of personal traumatic scripts [76] and the emotional Stroop test [77]. Anterior cingulate volume was also found to be lower in PTSD in two recent structural MRI studies [78,79]. Anterior cingulate morphometric and functional deficits are consistent with impairment in extinction as hypothesized above.

A large body of evidence suggests that hippocampal volume is reduced in PTSD [69,72,80–82], although exceptions have also been reported [70,71,83]. Smaller hippocampal volume may be particularly related to childhood physical or sexual abuse in patients with PTSD [84], or even depression [85]. Reduction in hippocampal volume may be related to deficits in declarative memory [86,87], and may be reversible and amenable to treatment with antidepressants [86]. Smaller hippocampal size may also be a permanent and premorbid vulnerability factor, unrelated to the actual expression of the disorder, as shown by a recent twin study of Vietnam veterans with and without PTSD [88]. A decrease in hippocampal size may be related to PTSD patients' ill-timed fear response. The enhanced and inappropriate fear response suggests a difficulty in integrating contextual stimuli to form a coherent representation of the environment actually related to the traumatic event [48]. To summarize, data from brain imaging studies in healthy controls and patients with PTSD as well as preclincal research support the involvement of mPFC, hippocampus and amygdala in perceiving, modulating and responding to fear associated stimuli. Deficits in these regions may underlie the pathophysiology of PTSD.

1.2. Neurochemistry of re-experiencing and emotional memory

Glutamatergic systems function as networks that sustain the associative functions of the cortex and hippocampus, the sensory relay operations of the hypothalamus, the danger alarming processing functions of the amygdala and basal forebrain and motivation response systems [89]. Glutamatergic neurotransmission is also central to CNS mechanisms of plasticity, such as long-term potentiation (LTP) or depression (LDP) and short-term potentiation (STP) [90]. These networks are all involved in the modulation of stress response and potentially in the pathophysiology of PTSD: impairment in NMDA mediated detection, registration and encoding of sensory traumatic input may contribute to the development of PTSD [91]. Fear conditioning and extinction are both dependent upon proper function of NMDA receptors in the amygdala [92], while consolidation of the memories for these associative learning processes may involve interplay of NMDA-mediated plasticity in prefrontal-amygdala circuits [93]. NMDA receptor effects in both fear conditioning and extinction are largely mediated by mitogen-activated protein kinase (MAPK) [94]. Recent work has further shown that concerted glutamatergic and gamma-aminobutyric acid (GABA) neurotransmission is required for extinction of conditioned fear [95]. Given the permissive role of NMDA neurotransmission in fear conditioning and extinction, it has been recently shown that both localized injection of the NMDA receptor partial agonist D-cycloserine (a partial agonist at the strychnine-insensitive glycine-recognition site on the NMDA receptor complex) into the amygdala as well as systemic administration of this compound enhanced extinction of the conditioned fear response [55]. Group II metabotropic glutamate receptor agonists reduce spontaneous and stress induced glutamate release [96]. Intra-amygdala infusions of the Group II receptor agonist LY354740 significantly disrupt fear-potentiated startle. The same rats were unimpaired when later tested without drug. Coadministration of the Group II receptor antagonist LY341495 prevented it this effect. Pretraining administration of LY354740 infusions also blocked learning [97].

BLA plasticity and expression of fear response are also regulated by input from the PFC and dopaminergic neurotransmission [98]. Integration of CS and US and the expression of conditioned fear response are enhanced by dopaminergic input and inhibited by the PFC [99]. Acquisition of the CS/US association requires activation of D2 dopamine receptors and is blocked by administration of dopaminergic antagonists (haloperidol). Once conditioning has been acquired, antagonism of dopamine receptors will not prevent expression of a conditioned fear response [100]. However, inhibitory input from the PFC can over-ride and attenuate the behavioral component of conditioned or non-conditioned fear response (for example, prevent expression of a 'flight or flight response'

to the barking of a familiar dog). Activation of D1 dopaminergic receptors reduces PFC inhibition on both acquisition and expression of fear response [101]. Thus, under normal conditions a balance between dopaminergic facilitation and PFC inhibition helps maintain the adaptive role of fear conditioning in management of stress. The relevance of these findings to processes in the human brain is supported by the findings of increased amygdala dopamine release during associative learning and performance of memory tasks [102].

The role of glucocorticoids in fear conditioning has been extensively studied [103]: basal levels of corticosterone, occupying hippocampal mineralocorticoid receptors (MRs), enable the expression of the unconditioned fear response (UR) after the initial unconditioned aversive stimulus (US). Increased corticosterone levels then act through glucocorticoid receptors (GRs) in the acquisition of both cue and context conditioned fear response. Once aversive conditioning has been established, corticosterone, via MRs, exerts a permissive action for the expression of the immediate conditioned fear response (CR) after exposure to a CS. Increased corticosterone brain GR-occupation then promotes processes underlying generalized fear response. Binding of corticosterone to brain MRs is a prerequisite for the extinction of passive avoidance behavior, whereas GRs are involved in the extinction of active avoidance behavior. Potentiation of fear response appears to be dependant upon GRs. Thus, MRs and GRs are jointly involved in the different stages of associative learning. Impaired conditioning and extinction processes, as in PTSD, may represent MR/GR functional imbalance [103] rather than an absolute abnormality in the level of any particular component of the limbic–hypothalamus–pituitary–adrecortical (LHPA) axis.

Exposure to a conditioned fear stimulus increases serotonin (5HT) metabolism in the mPFC, nucleus accumbens, and amygdala [104]). Microinjection of 5HT into the amygdala appears to enhance conditioned fear responding, while 5HT injection into the peri-aquaductal-gray (PAG) inhibits unconditioned fear response [105]. 5HT1A and 5HT2A are the two serotonergic receptors most often implicated with anxiety. Their anxiogenic and anxiolytic properties are not yet fully understood, and may vary with location, stimulus and interaction with other neurotransmitters or peptides [106]. Graeff [105] hypothesized that the serotonergic innervation of the amygdala and the hippocampus mediates anxiogenic effects via 5HT2A receptor stimulation, whereas serotonergic innervation of hippocampal 5HT1A receptors suppresses the anxiety response to unpredictable aversive events. Potentially compatible with this hypothesis, 5HT1A receptor knockout mice exhibit behaviors consistent with increased anxiety and fear, and chronic administration of 5HT1A receptor partial agonists exerts anxiolytic effects in generalized anxiety disorder [107]. Gross et al. [108] have recently shown the anxiolytic effects of 5HT1A receptors are predominantly mediated by forebrain postsynaptic receptors, and that early postnatal establishment of 5-HT1A transmission is essential for establishing normal anxiety behaviors in adulthood. In contrast to the anxiolytic effect of 5HT1A receptors, modulation of stress activated hypothalamic–pituitary–adrenal (HPA) axis hormonal response is apparently facilitated by activation of 5HT2A receptors that stimulate secretion of adrenocorticotrophic hormone (ACTH), oxytocin, prolactin, and corticosterone [109]. 5HT1A is the most abundant serotonin receptor in the hippocampus, where it is colocalized with glucocorticoid and mineralocorticoid receptors [110]. Postsynaptic 5HT1A receptor gene expression is under tonic inhibition mediated largely by mineralocorticoid receptors (MR) [111]). This regulatory steroid effect is rapid, and 5HT1A mRNA levels markedly decrease within hours of mineralocorticoid receptor stimulation [110]. Preclinical research has shown that psychological stress may increase MR levels in the hippocampus as soon as 8 h following exposure to stress [112]. Such increase in MR could reduce 5HT1A density and contribute to the stress response.

Given the potential rapid alterations in 5HT1A receptor densities following exposure to stress, human brain imaging of 5HT1A (and possibly 5HT2-A) receptors could provide measures of baseline and stress related 5HT1A receptor concentrations in healthy and anxious subjects. A preliminary receptor binding study reports a significant negative correlation between 5HT1A binding potential and indirect measures of anxiety in the dorsolateral prefrontal cortex, anterior cingulate cortex, parietal cortex, and occipital cortex. [113]. In a recently completed study Neumeister et al. found [114] significantly reduced 5HT1A receptor density and binding potential in the anterior and posterior cingulate cortices and the raphe nucleus of patients with panic disorder compared to healthy control subjects. These findings are consistent with preclinical research as described above and with clinical trial data showing anxiolytic properties of partial 5HT1A agonists.

2. Avoidance, numbing and interpersonal constriction: relevance of animal models

The second cluster in PTSD comprises two major types of symptoms: Avoidance symptoms, both emotional avoidance, i.e. of thoughts, feelings or conversations associated with the trauma, and physical avoidance, i.e. of activities and people or places that may recall the event, and depression like symptoms such as emotional numbing, loss of interest, social avoidance and withdrawal, and a sense of foreshortened future. Such symptoms are similar to the 'learned helplessness' description of animal behavior after exposure to severe stress [115–117]. This similarity has already been noted before [118]. The definitions used in the literature to describe the stress that induces learned helplessness are not consistent, with stress described as

'inescapable', 'unavoidable' and 'uncontrollable', as well as 'chronic' and 'continuous'. All these terms denote exposure to significant stress, and convey the idea that learned helplessness is observed after major stress, presumably accompanied by severe subjective distress. For clarity and consistency we will refer to the mode of stress that produces learned helplessness as inescapable stress. The animal model of inescapable stress followed by learned helplessness has been used as an animal analogue of depression, anxiety and/or PTSD [117]. We find this model particularly suitable to describe this symptom cluster of PTSD (Fig. 1 and Table 1).

Learned helplessness is a response unique to 'inescapable', in contrast to 'escapable' stress. This response mode is ethologically adaptive for animals in situations where both 'fight' and 'flight' options are ineffective, for example, when confronted by an 'inescapable' predator. Often the predator would judge his prey to be dead or ill and lose interest [119]. In addition, the complete withdrawal and inactivity in 'learned helplessness' have been suggested to serve a 'replenishing' function, ostensibly after active coping resources have been exhausted. Recent research suggests that learned helplessness has neuroprotective capabilities [120] (see below).

As described above, the essentially adaptive mechanism of fear conditioning becomes maladaptive in PTSD, the CS becomes generalized, unpredictable and uncontrollable, and a person feels constantly threatened. This state is comparable to inescapable stress and results in learned helplessness behavior. Exposure to inescapable stress may also be related to the increased comorbidity between PTSD and substance abuse disorders [121]. It has been shown that inescapable, but not escapable stress, potentiates morphine's rewarding properties [122]. In veterans with PTSD, but not in veterans without PTSD, exposure to visual combat stimulus resulted in a significant analgesic effect, which was prevented by administration of pre-exposure naloxone [123]. These findings, together with the observation that initial drug use in PTSD is often an attempt at self-medication [121], may begin to provide an explanation regarding why patients with PTSD are more vulnerable to abuse and addiction.

The standard measure of whether learned helplessness has been attained after stress exposure is 'delayed escape' [124]. It is assessed by determining the time required for animals to learn that a given behavior will terminate shock/stress. Learned helplessness animals require a significantly longer time to learn this [124], to the extent that 'delayed escape' has become perhaps the foremost criterion for learned helplessness. Research performed by the Anisman laboratory has shown that a specific strain of mice (BALB/cByJ) is particularly susceptible to exhibit delayed escape after inescapable stress [125]. Exposure to inescapable stress and the resultant learned helplessness has been shown to enhance fear conditioning [126,127]. The continuous reexperiencing and resultant distress in PTSD, together with emotional memory storage mechanisms such as reconsolidation [30], suggest that fear conditioning in PTSD is not a one time event but rather a continuous accumulative process. Delayed escape behavior and facilitation of fear conditioning enhance this process even more, and can be conceived as providing 'positive feedback' to the process of fear conditioning acquisition. An additional similarity between PTSD and the animal model of inescapable stress—learned helplessness is the 'inescapable' nature of the stress in the animal model and the person's response to the traumatic stressor ('helplessness, fear or horror') in criterion 'A2' of DSM-IV PTSD.

2.1. Neural circuitry of inescapable stress and learned helplessness

The neurocircuitry of inescapable stress has not been definitely described, but recent research enables presentation of a preliminary 'working hypothesis' of such neurocircuitry (Table 1). The brain region most closely associated with mediating incapable stress and learned helplessness may be the predominantly serotonergic dorsal raphe nucleus (DRN), with the caudal part of this nucleus apparently particularly involved [128–130]. The DRN provides a large portion of the serotonergic projections ascending to the cortex, hippocampus, amygdala (particularly basolateral), hypothalamus and other forebrain and midbrain structures [131]. The widespread nature of DRN projections provides a framework for the extensive effects of 5HT on behavior. Lesions of the DRN [132] as well as pharmacological inhibition of DRN serotonergic activity during inescapable stress prevent the occurrence of the behavioral changes that ordinarily follow it [133,134]. The habenular complex appears to be closely involved in modulation of inescapable stress neurocircuitry [129]. It projects to the DRN and utilizes the excitatory amino acid aspartate to excite DRN neurons and increase 5HT levels [135]. Lesions in the habenula eliminated the differential rise in DRN extracellular 5HT levels and the differences in escape latency between animals exposed to escapable, compared to inescapable, stress [129].

Basal levels of 5HT in animals were elevated after 'inescapable', but not after 'escapable', stress in the basolateral nucleus of the amygdala (BLA) [132,136] and previously inescapably shocked animals exhibited an exaggerated 5-HT response to novel aversive stimuli. Large electrolytic amygdalae lesions have no effect on escape latency, but bed nucleus of the stria terminalis (BNST) lesions completely block the escape deficits produced by inescapable shock [137]. The BNST receives dense projections from the dorsal raphe nucleus [131]. Since it is particularly involved in the neurocircuitry of anxiety, mainly relevant to the arousal cluster of symptoms (see below), the relationship between BNST and learned helplessness behavior provides an insight

into potential interrelations of symptom clusters in PTSD. Differential serotonergic response to inescapable, compared to escapable stress was also seen in the hippocampus and periaqueductal gray [138], regions that receive extensive serotonergic projections from the DRN. Delayed escape learning, typical of learned helplessness, was correlated with alterations in hippocampal morphology in the BALB/cByJ environmentally sensitive strain of mice [139]. Facilitation of serotonergic neurotransmission in the dorsal hippocampus can prevent the development of learned helplessness [140]. This effect is probably mediated through the activation of post-synaptic 5-HT1A receptors. Administration of CRH prior to immobilization stress facilitated (primed) long-term potentiation of population spikes (PS-LTP) in the mouse hippocampus and enhanced context-dependent fear conditioning [141]. This suggests that preexisting anxiety in animals (perhaps an equivalent of the human 'anticipatory' anxiety) enhances the permissive effects of inescapable stress upon fear conditioning. A significant decrease in hippocampal cell proliferation was found in adult rats exposed to inescapable stress compared to non-stressed animals. Administration of fluoxetine blocked the decrease in cell proliferation and reversed the deficit in escape latency observed in animals exposed to inescapable stress [142]. Increased escape latency, the hallmark of learned helplessness, reflects a deficit in spatial orientation in experimental animals. Impaired processing of environmental stimuli results in untimely expression of the fear response and indicates loss of the adaptive function of fear conditioning. Both alterations in the protective behavioral pattern are indicative of hippocampal malfunction. This may be of relevance given the findings of reduced hippocampal volume findings in PTSD.

The effect of inescapable stress on the dopaminergic (DA) system has traditionally been viewed as an analogue for depression, more than for the anxiety type of disorders. However, given the overlap between depression and anxiety symptoms in this PTSD cluster, and the difficulty in relating animal behavior to 'depression' or 'PTSD', learned helplessness behavior may well be considered at least a partial model for PTSD. Dopaminergic innervation of the basolateral and central nuclei of the amygdala, the medial prefrontal cortex, and other limbic regions is highly responsive to stress and may be altered by stress [143,144]. Modulation of inescapable stress induced DA activation in the mesocortical, mesostriatal and mesoaccumbens is probably performed in the amygdala [120,145,146], particularly regarding conditioned responses, possibly in a similar manner to regulation of the serotonergic stress response system (see above) in similar circumstances. In both cases a conditioned fear stimulus takes on the attributes of an inescapable stressor.

2.2. Neurochemistry of inescapable stress and learned helplessness

Pretreatment of animals with selective serotonin reuptake inhibitors (SSRIs), as well as tricyclic antidepressants before exposure to inescapable stress prevents the behavioral syndrome of learned helplessness. Administration of these agents once learned helplessness is acquired will also reverse most symptoms. Inescapable tailshock led to greater serotonergic neural activity in serotonergic neurons in the DRN than did escapable tailshock [128]. There is some preliminary evidence for abnormalities in serotonergic function in subjects with PTSD. Challenge studies probing the serotonergic system using mCPP demonstrated that a subgroup of patients with PTSD develop anxiety and flashbacks upon provocation with this agent [147]. However, Davis et al. [148] used the serotonin-releasing agent and reuptake inhibitor D-fenfluramine in PTSD patients and demonstrated a significantly lower prolactin response compared to control subjects, suggesting reduced central serotonergic sensitivity. Peripheral serotonergic studies report decreased platelet paroxetine binding [149,150] and low platelet-poor plasma concentrations of serotonin in patients with combat related PTSD [151] and conclude that serotonergic mechanisms may play a role in the pathophysiology of PTSD.

Other neurotransmitters have also been linked to the neurochemistry of inescapable stress. Microinjection of a non-selective CRH receptor antagonist into the DRN blocked the inescapable stress-induced behavioral changes when administered before inescapable stress but not when administered before later behavioral testing. Intra-DRN administration of CRH (in the absence of inescapable stress) mimicked the effects of inescapable stress, interfered with escape behavior and increased fear conditioning [130]. Moreover, systemically administered CRH receptor antagonists given before inescapable shock [152] or before escape testing [153] also block escape deficits in this paradigm. CRH apparently mediates and modulates serotonergic neurotransmission during severe inescapable stress, affecting the behavioral manifestations of the response to such stress [154]. Furtheremore, both the novel SSR125543A CRH(1) antagonist and the better known CRH(1) receptor antagonist antalarmin displayed limited efficacy in several models of anxiety induction but produced clear-cut anxiolytic activity in models of anxiety involving traumatic experience (social defeat) and inescapable stress [155].

Norepinephrine release in the DRN may also be involved in modulating the behavioral consequences of exposure to inescapable stress. A selective alpha1 adrenoreceptor antagonist (benoxathian) prevented the impairment in escape responding produced by inescapable shock [156]. Enhancement of conditioned fear produced by prior inescapable shock was attenuated by benoxathian administered before behavioral testing. Noradrenergic input to

the DRN therefore, appears necessary to produce the behavioral effects of inescapable tail shock [156]. Glutamatergic input to the DRN at the time of inescapable stress also seems necessary to produce the behavioral response of learned helplessness and possibly produces long-lasting changes in DRN sensitivity [157]. The plasticity in the DRN may be related to inescapable stress-induced delay in escape performance and enhancement in conditioned fear responding. Injection of NMDA antagonists to the DRN, but not to nearby loci, prevented the characteristic learned helplessness response to inescapable stress [157]. Opiate agonists and antagonists also modulate the impact of inescapable stress through the DRN [158]. The opiate antagonist naltrexone injected into the DRN immediately prior to inescapable stress prevented both delayed escape and enhancement of fear conditioning. Conversely, the opiate agonist morphine, in combination with a subthreshold number of 20 inescapable stress trials, induced an escape deficit and enhanced conditioned fear [158]. Electrolytic lesions of the DRN prevented this effect. Exposure to stress augments the locomotor responses to cocaine challenge, partly through altering dopaminergic release. This example of cross-sensitization may be relevant both to the pathogenesis of PTSD [38], and to the increased abuse potential in the disorder [159].

Even minor stress increases dopamine release and turnover in the prefrontal cortex in the absence of overt changes in other mesotelencephalic dopaminergic innervated regions [104]. Stress of greater intensity enhances dopamine (DA) release and turnover in other areas as well [104]. Inescapable/uncontrollable stressors used to simulate depressive-like responses in animal models [160] promote not only a strong activation of the mesocortical DA system but also inhibition of the DA mesoaccumbens and mesostriatal pathways [161]. Recent studies have demonstrated that genetic susceptibility of the mesocortical DA system to inescapable stress (forced swim test; FST) influences the vulnerability of the animal to express the syndrome of learned helplessness (or 'despair') [162]. Similarly, the environmentally responsive (BALB/cByJ) mice strain mentioned above exhibits hypercorticoid secretion and alteration in central dopaminergic and noradrenergic levels and activity [163,164]. Thus, genotypes for 'learned helplessness prone' and 'learned helplessness resilient' could largely determine the behavioral outcome to an identical stressor in respective animal strains. Several twin studies have been performed in PTSD. Reports based upon the Vietnam twin registry demonstrated a genetic contribution of about 30% to the expression of PTSD symptoms after exposure to combat trauma [165, 166]. The same magnitude of inherited effect was recently demonstrated by a study examining non-combat-trauma PTSD [167]. The first molecular-genetic study in PTSD, reports an association between the dopamine transporter (DAT) gene and PTSD, with a significant excess of nine repeat allele among PTSD patients [168]. The DAT has been previously associated with several behavioral phenotypes including attention deficit hyperactivity disorder and tobacco addiction. Future research in PTSD should incorporate brain imaging of the DAT and D2 receptors, seeking cerebral anatomical and functional correlates of dopaminergic receptor and transporter genetic polymorphisms. Peripheral human PTSD studies have shown abnormalities in peripheral measures of dopamine, such as increased urinary excretion and [151,169–171] and higher levels of plasma dopamine [172]. Urinary excretion of DA correlated with the severity of PTSD symptoms [171].

Recent work regarding the learned helplessness paradigm ties neuronal sensitization to the behavioral impairment that follows unpredicted and inescapable stress [120]. This model suggests that serotonin and corticosterone secretion in the basolateral amygdala, due to inescapable, continued stress, eventually deplete GABA, removing a major form of inhibition upon excitatory glutamate transmission in the amygdala, hippocampus, and frontal cortex. Continuation of, or re-exposure to stress (as in shuttle escape testing 24 h after inescapable stress) results in unregulated excitation of glutamate neurons. Secretion of the purine nucleoside adenosine inhibits metabolic activity in depleted cells and facilitates the recovery of energy homeostasis. This form of regulation is now well recognized for its neuroprotective benefits, and can explain the sensory unresponsiveness, cognitive dullness, and behavioral depression that characterizes the state of learned helplessness [120]. Compatible with this model, in an early experiment GABA prevented subsequent development of learned helplessness when injected into the frontal cortex or hippocampus. Microinjection of GABA to the hippocampus also reversed learned helplessness when injected after inescapable stress [173]. The involvement of hippocampal GABA receptors in learned helplessness was also suggested by the finding that microinjection of bicuculline, a GABA(A) receptor antagonist, into the hippocampus induced learned helpless behavior in naïve, non-stressed rats [174]. Injection of benzodiazepine (BZD) inverse agonists into the DRN also induced helpless behavior in naïve rats [175]. Animals exposed to inescapable stress during a time period between 7 days and several months developed a 20–30% decrease in BZD receptor binding in frontal cortex [176] cerebral cortex [177,178] and hippocampus [177,179,180]. After exposure to inescapable stress, learned helpless rats had increased densities of GABA(A) receptors in the septum while rats that did not become helpless had decreased GABA(B) receptor densities [181].

In human studies, increased levels of the GABA(A) antagonists dehydroepiandrosterone (DHEA) and its sulfate derivative (DHEAS) were found in patients with PTSD compared with healthy control subjects [182]. Lower distribution volumes of benzodiazepine receptor binding were found in the prefrontal cortex of veteran PTSD patients than in comparison healthy subjects. These findings are consistent with fewer benzodiazepine receptors and/or

reduced affinity of receptor binding in the medial prefrontal cortex in patients with PTSD [183].

3. Increased arousal and persistent anxiety

This cluster comprises symptoms of persistent anxiety and motor hyper-responsivity. Patients suffer from difficulties in sleep and concentration, are irritable, hyper-vigilant and 'jumpy'. They lose their basic sense of safety [184]. As described above, the adaptive function of fear conditioning, to distinguish between safe and unsafe and facilitate identification of danger, fails in PTSD. This failure becomes manifest by the generalization of stimuli that can trigger the fear response. Parallel to this is an expansion of the threatening context, to the extent that almost every place becomes unsafe. Danger becomes both imminent and unpredictable. This results in a state of continuous anticipatory anxiety, increasing patient vulnerability to further insult.

The autonomic nervous system is the effector limb through which the brain provides a rapid response to stress [185] (Table 1). When an individual is threatened, cardiac output and respiration are accelerated, catabolism is increased and blood flow is primarily directed to the brain, heart and muscles. This response is regulated by the sympathetic and parasympathetic nervous systems, offering control of a wide range of physiological function [1]. Involuntary prolongation of this response in the absence of external threat is an additional example of the transformation of an initially adaptive response into a maladaptive and taxing condition. This condition is often addressed as 'hyperarousal' and comprises symptoms suggestive of persistent anxiety as well as autonomic hyper-responsivity. Hyperaroused patients exhibit elevated baseline heart rate (HR) and skin conductance (SC), slower SC response habituation, exaggerated startle reactivity [186–189] and reduction of the P200 response to loud sounds [186].

A distinction is traditionally made between *fear*, an extreme, time limited emotion associated with a clearly identifiable imminent threat, and *anxiety*, a generalized, continued apprehension of an imminent, but unidentified hovering threat [190,191]. These conditions may be mediated by partly different neurocircuitry [137] (see below). Patients with PTSD exhibit both fear and anxiety, which exacerbate one another: Here again is an example of the vicious cycle complicating PTSD, where heightened anxiety and arousal make an individual prone to experience fear (UCR) from less well-defined, unpredictable stimuli (CS), further exacerbating baseline anxiety, making the individual more vulnerable to experience another fear condition, and so forth [20,192]. It has been shown that the cumulative physiological response to both anxiety and fear related stimuli is greater than the response to either stimulus separately [137]. Full-blown fear symptoms are currently grouped into the reexperiencing cluster, whereas anxiety symptoms are considered part of the hyperarousal cluster (Table 1).

The concepts of sensitization and habituation have been mentioned above, but are of particular relevance in this symptom cluster (Fig. 1). Repeated presentation of a stimulus may result in a progressively decreasing response, termed 'habituation', or a progressively increasing response, termed 'sensitization'. Interestingly the same stimulus can cause habituation at one time and sensitization another time. Both mechanisms are forms of non-associative learning [193], and may be prompted by environmental, behavioral, physical and neurochemical stimuli. Repeated presentation of a stimulus may also result in an increased response to novel stimuli, a phenomenon termed 'cross sensitization'. Enhanced sensitization and cross sensitization may also contribute to the vulnerability for PTSD in individuals with childhood trauma exposure [194].

Brain imaging studies show a reduction of initially elevated rCBF response in areas involved in the processing of repeated sensory stimuli [195–197]. fMRI studies of fear conditioning in healthy subjects have shown habituation of the amygdala to repeated CS + presentations [61]. Likewise, a significant stimulus (CS − or CS +) by time interaction, with rapid adaptation to CS + in the amygdala and hippocampus, was reported in an aversive differential trace conditioning paradigm [198]. Rapid habituation of the amygdala was observed in single cell recordings in rodents [199]. In contrast, delay or absence in habituation is often reported in PTSD. Habituation of the amygdala was not reported for patients with PTSD exposed to masked fearful faces [200]. In studies of the autonomic components of the acoustic startle response, patients with PTSD show a delay in habituation of skin conductance responses [186,201,202]. Habituation of the P1 midlatency auditory evoked potential in PTSD was significantly diminished compared to combat-exposed controls and other control groups [203]. In keeping with our model, results of a prospective study that assessed psychophysiologic responsiveness over a 4-month period following a traumatic event suggest that increased heart rate response and reduced habituation develop parallel to PTSD [201]. These findings are consistent with our model, where enhanced sensitization and delayed habituation play a major role in the pathophysiology of PTSD.

3.1. Neurocircuitry of arousal and anxiety

The brain regions mediating the association between external stimuli processing and incorporation of emotional valence have been described in Section 1. In this section we will focus upon the efferent components of the anxiety and fear neurocircuitry (Table 1). It has been recently proposed that the neural systems mediating fear and anxiety are at least to some extent separate [137]. Lesioning of the BNST and the central nucleus (CE) of the amygdala block different types of conditioned fear responses, with BNST primarily affecting slower onset and prolonged responses and the CE

modulating rapid, brief responses [204]. Thus, the CE is considered to predominantly mediate fear conditioned responses, while the BNST appears to be involved mainly in more prolonged anxiety response patterns. The BNST and CE both receive afferent innervation from the BLA, and project to a common set of target areas that mediate many of the behavioral, autonomic, and electrophysiological consequences of fear and anxiety. Downstream target regions that receive projections from the BNST and CE include the lateral and paraventricular nuclei of the hypothalamus (the latter mostly innervated by the BNST), locus coeruleus (LC), ventral tegmental area, nucleus tractus solitarius, caudal ventrolateral medulla, dorsal motor nerve root of the vagus nerve and nucleus ambiguous, parabrachial nucleus and periaquaductal gray (PAG) [10,205]. Since efferent regions of CE and BNST largely overlap, the manifestations of fear and anxiety are very much similar, and differ mostly in duration and magnitude.

Fear and anxiety activate brain noradrenergic function. The LC is the major source for NE innervation, a critical component of the brain's alerting and vigilance system, and highly connected to many central cortical and subcortical structures, such as the hippocampus, amygdala, hypothalamus, prefrontal cortex, PAG and various brainstem nuclei. The anterior cingulate also has extensive connections with brain regions involved in arousal and regulation of the autonomic nervous system [206]. The exact nature of this association has not been fully elucidated [207,208], but is thought to be the major cortical regulator of habituation in subcortical regions [209], and its malfunction may be a major cause of the attenuated habituation [202] and psychophysiologic arousal [186,210] observed in PTSD.

Animal studies have shown a significantly higher number of Fos positive neurons after exposing preshocked rats to a different, moderate stress, compared to never-shocked controls, in many brain areas: nucleus accumbens, bed nucleus of the stria terminalis, basolateral amygdala, CA1 area of the hippocampus, paraventricular hypothalamic nucleus, locus coeruleus and others [211]. Likewise, repeated exposure to moderate stress induced a significant increase in CRH immunoreactivity in the paraventricular nucleus of the hypothalamus, the median eminence and the central amygdala [212], suggesting sensitization of CRH in specific brain regions. Long-term sensitization of blood pressure responses was also demonstrated by the same group [213], reflecting an observable component of this phenomenon. Past exposure to inescapable stress, as described above, also results in a long-lasting sensitization, as illustrated by an elevated startle response to auditory tones [214]. Administration of four anxiogenic drugs (FG-7142, yohimbine, *m*-chlorophenylpiperazine (*m*CPP), and caffeine) increased Fos-like immunoreactivity in seven brain areas: central nucleus of the amygdala, bed nucleus of the stria terminalis, lateral septum, paraventricular nucleus of the hypothalamus, lateral hypothalamus, infralimbic and prelimbic cortex [215]. All drugs but one (mCPP) also increased Fos expression in the basolateral and medial amygdala, the dorsomedial hypothalamus, cingulate cortex, and parts of the motor cortex. Overall, it seems that post-stress sensitization as well as administration of anxiogenic agents activate a set of predefined and rather constant brain regions associated with autonomic nervous system arousal.

3.2. Neurochemistry of increased arousal

Interactions between the HPA axis and the noradrenergic systems play a major role in regulating the autonomic response to stress. The LC is a critical component of the brain's alerting or vigilance system. Rapid activation of the LC/NE system facilitates the organism's ability to respond effectively in dangerous situations [216]. Secretion of CRH increases LC neuronal firing activity, resulting in enhanced NE release in a variety of cortical and subcortical regions. Conversely, NE release stimulates CRH secretion in the PVN (the nucleus containing the majority of CRH-synthesizing neurons in the hypothalamus). CRH release in the PVN stimulates ACTH secretion from the pituitary and cortisol secretion from the adrenal glands. The rise in plasma cortisol concentrations acts through a negative feedback pathway to decrease both CRH and NE synthesis at the level of the PVN. Glucocorticoid-mediated inhibition of NE-induced CRH stimulation may be evident primarily during stress, rather than under resting conditions, as an adaptive response that restrains stress-induced neuroendocrine and cardiovascular effects. Levels of NE, cortisol, and CRH appear to be related within a functional system that offers a homeostatic mechanism for responding to stress. Electrical stimulation of the LC produces a series of behavioral responses similar to those observed in naturally occurring or experimentally induced fear. These behaviors are also elicited by administration of drugs such as yohimbine and piperoxone, which activate the LC by blocking α_2-adrenergic autoreceptors. The sensitivity of α_2-adrenoreceptors also appears increased in PTSD. Subjects with combat-related PTSD show increased behavioral, chemical, and cardiovascular responses to yohimbine, relative to healthy controls, and yohimbine administration resulted in altered metabolic activity in the orbital, temporal, parietal, and prefrontal cortices in healthy controls relative to PTSD subjects [217].

Considerable evidence indicates that noradrenergic function is abnormal in PTSD. Women with PTSD secondary to childhood sexual abuse show elevated 24-hour urinary excretion of catecholamines [169]. Men with PTSD resulting from a motor vehicle accident exhibited elevated urinary levels of epinephrine, NE, and cortisol [218]. Maltreated children with PTSD excreted greater amounts of urinary dopamine, NE, and cortisol over 24 h than controls, with the urinary catecholamine and cortisol output positively correlated with the duration of PTSD trauma and the severity of PTSD symptoms [171]. Geracioti [219] found that cerebrospinal fluid NE concentrations are abnormally elevated in

PTSD. Platelet α_2-adrenoreceptor density, platelet basal adenosine, isoproterenol, forskolin-stimulated cAMP signal transduction, and basal platelet monoamine oxidase (MAO) activity) were decreased in PTSD, findings hypothesized to reflect compensatory responses to chronically elevated NE release [28].

Drugs that decrease the function of the LC by interacting with inhibitory opiate (morphine), benzodiazepine (diazepam), and α_2-(clonidine) receptors on the LC decrease fearful behavior. The responsiveness of LC neurons to novel stressors is enhanced by previous exposure to stress and may constitute a form of behavioral sensitization. Sensitization and habituation have mostly been demonstrated for the HPA axis, dopaminergic and noradrenergic systems. A recent study [220] reports that only an MR antagonist, but not a GR antagonist, blocked habituation of corticosterone response to repeated restraint stress, a common means for evaluating the animal correlate of response to a psychological stressor. The MR antagonist did not alter the corticosterone response to a CRH challenge and had no effect on corticosterone response to the first restraint stress indicating it does not dampen the overall responsivity of the system. Two studies document increased cerebral spinal fluid (CSF) CRH in patients with PTSD relative to healthy controls [221,222]. However, cortisol levels in these samples were not increased, as is the case in most PTSD studies. Furthermore, CSF-CRH concentrations are not correlated with plasma cortisol [221,223,224]. In contrast, increased pituitary and adrenal reactivity to CRH and ACTH was recently reported in premenopausal women with PTSD [225]. As with peripheral levels of cortisol, this is in agreement with some [226,227] but not all [228,229] previous reports.

Dopaminergic innervation in the nucleus accumbens and medial prefrontal cortex are particularly sensitive to repeated stress [230] and sensitize easily. Benzodiazepine anxiolytics prevent selective increases in dopamine utilization in mPFC following mild stress. Anxiogenic benzodiazepine inverse agonists exert an opposite effect. Selective activation of mPFC dopamine neurons can also be induced by intracerebroventricular injection of CRH [231]. Sensitization has been paralleled to kindling, and may be relevant to the pathogenesis of PTSD [38].

Neuropeptide Y (NPY) is a 36 amino acid peptide neurotransmitter that is co-localized with NE in the LC, amygdala, hippocampus, PAG and PFC. One of NPY's central and peripheral actions is to inhibit release of the neurotransmitter with which it is co-localized. In numerous preclinical studies, NPY has been shown to inhibit the firing rate of LC neurons and to inhibit release of NE through actions at the presynaptic receptor. It has accordingly been shown to exhibit anxiolytic properties in animal models of anxiety [232]. Dopamine seems to be the most important modulator of NPY biosynthesis and expression. Blockade of dopaminergic receptors first induces a decrease and after prolonged treatment an increase in NPY mRNA [233]. Preclinical data further shows that chronic stress exposure may result in the development of low baseline levels of NPY as well as a blunted NPY response to subsequent stress [234]. Recent evidence suggests that corticotropin-releasing factor (CRH) and NPY exert a reciprocal regulation of responsiveness to stressful stimuli, possibly via an interaction of these two systems in the amygdala [235]. It appears that NPY leads to inhibition of cAMP production while CRH stimulates cAMP production. CRH and NPY may, therefore, counter-regulate each other in amygdalar neurons via reciprocal effects on protein kinase A pathways [236]. Therefore, sensitization induced increases in LC firing and NE turnover may be related to stress-induced (or otherwise) decreases in plasma NPY. In a human study [237], subjects with PTSD had lower baseline plasma NPY and blunted yohimbine-stimulated increases in plasma NPY compared with healthy control subjects. This suggests that stress-induced decreases in plasma NPY may mediate noradrenergic system hyper-reactivity observed in PTSD, and that high NPY levels may offer protection against PTSD.

Serotonergic projections from the dorsal raphe nucleus inhibit firing of the LC, whereas noradrenergic projections from the LC have an excitatory effect on cell bodies in the dorsal raphe [106]. The balance between 5HT and NE thereby affects the rate of discharge of the LC. SSRIs, by restoring serotonergic tone to the LC, might dampen its firing rate and in this way decrease excitatory input to the amygdala [238]. Support for this effect comes from a study demonstrating that effective antipanic treatment with an SSRI normalized dysregulation of noradrenergic function [238].

Animal research has also shown that limbic NMDA receptors mediate lasting increases in anxiety-like behavior produced by the stress of a single predator exposure [239]. Elevation in the amplitude of the acoustic startle reflex response after exposure to a fear-inducing stimulus in animals also appears to be modulated by the NMDA receptor system [240], reminiscent of the fear-potentiated startle phenomenon in PTSD [241]. Therefore, it appears that NMDA receptors may partake in sensitization in PTSD as well. It has been assumed that stress effect on hippocampus is largely mediated by glucocorticoids and requires NMDA receptor activation. However, recent preclinical findings demonstrated that early life CRH infusion was associated with a reduced number of hippocampal CA3 neurons and up-regulation of CRH expression in adults [242]. This effect does not require glucocorticoids, involves interaction with glutamatergic mechanisms and enhanced calcium cell entry. It suggests that the elevated CRH levels documented in PTSD, as described above, may directly contribute to the reduced hippocampal volume observed in this disorder.

Recent work has also suggested a role for BDNF in mediating fear conditioning. BDNF is a member of the neurotrophin family of peptides and has been shown to support neuronal growth, differentiation, and survival in

the developing and adult hippocampus. It is highly concentrated in the dorsal hippocampus, including the dentate gyrus. Treatment with antidepressant drugs upregulates BDNF expression in animals [243] and humans [244]. It has been demonstrated that stress can decrease the expression of BDNF mRNA in the dentate gyrus and pyramidal cell layer of hippocampus [245,246]. This reduction in BDNF levels is apparently mediated by stress-induced glucocorticoid increases and/or increase in serotonergic neurotransmission [245]. Downregulation of BDNF mRNA in dentate gyrus of the hippocampus has been reported in rats re-exposed to prolonged traumatic cues [247]. This suggests that persistent stress might lead to reduced BDNF levels and subsequent structural damage of the hippocampus. The association between BDNF levels and hippocampal function may also be related to a recently demonstrated functional polymorphism of BDNF, in which activity-dependent secretion of BDNF was related to memory and hippocampal function [248].

We have described the major neurobiological mechanisms of PTSD, and the neuroanatomy and neurochemistry that enable their subsistence. In Section 4, we will try to implement this understanding to suggest potentially effective pharmacological agents for the treatment of PTSD.

4. Implications for the discovery and application of novel pharmacotherapeutics

Pharmacotherapy for PTSD is in its initial stages. Selective serotonin reuptake inhibitors (SSRIs) are the only medications currently approved by the FDA for treatment of PTSD. Other, previously administered psychopharmacological agents, including tricyclic antidepressants have not been similarly effective [249]. Although the clinical improvement attained by SSRIs is significant, many patients remain symptomatic after treatment [250–253]. Since a single agent is rarely capable of providing full relief for PTSD, several compounds are often used, reducing compliance and increasing adverse events.

A cardinal issue in therapeutic intervention is timing. After exposure to severe trauma, most individuals are preoccupied with the traumatic event and exhibit some degree of anxiety, arousal and/or emotional numbness and withdrawal and [4]. In most trauma survivors the severity of this condition diminishes within days or weeks. Nevertheless, this symptomatology coupled with common lore that early intervention may ‘prevent’ deleterious consequences, led to the frequent practice of ‘psychological debriefing’ in the acute aftermath of trauma. Only several years later the futility, and perhaps even risk, associated with this treatment emerged [254,255]. Similarly, a retrospective report comparing prognosis of subjects administered high potency benzodiazepines with equally symptomatic untreated individuals found a significantly higher rate of PTSD in the treated group [256]. In contrast, preliminary experience in treating acutely traumatized subjects with the beta adrenergic propranolol has been more favorable [257,258] (see below). Peritraumatic anxiety and withdrawal symptoms are compatible with our model and usually short-lived, and should be considered adaptive. It is questionable whether they should be considered an objective for treatment. However, unremitting symptoms should definitely be treated. It has been shown that subjects with persistent severe symptoms during the first month after trauma (i.e. meeting criteria for acute stress disorder, (ASD)) are at high risk to develop chronic PTSD if left untreated [259]. Choice of treatment, at least inasmuch as pharmacological treatment is concerned, is not simple. For example, ASD symptoms of arousal and dissociation are often thought to reflect hyper-glutamatergic neurotransmission. This may suggest treatment with benzodiazepines. However, our model for PTSD assumes that delay in extinction and/or impairment in recognition of safety cues contribute to the evolution of PTSD. Both are learning processes, reflect CNS plasticity and are glutamate dependent. Benzodiazepine enhanced inhibitory GABAergic neurotransmission could further impede extinction and identification of safety cues and exacerbate ASD/PTSD, in keeping with the study described above [256].

Empirical data on pharmacological interventions in PTSD is wanting. Many questions regarding judicious usage of medication cannot yet be answered: Are choice and efficacy of medication dependent upon PTSD phenomenology? Are choice and efficacy of medication dependent upon type of trauma? Should the same compounds be used in the acute and chronic conditions? How long should medication be administered? These questions remain mostly unanswered. The compounds presented below target elements of the neurobiological model for PTSD described above (Table 2). For the most part, information regarding drug effect was obtained from animal experiments. Some treatment trials were performed in humans, only a few in patients with PTSD. The list of potential therapeutic agents compiled below is not exhaustive, and requires laborious research until available for clinical use, if at all. Until this occurs, this review should be considered preliminary and somewhat speculative in nature.

4.1. CRH antagonists

CRH has traditionally been implicated in the anxiety and hyperarousal symptoms of PTSD, and, within the model presented above, also in facilitating traumatic memory consolidation and mediating 5HT neuronal activity in the DRN in the context of learned helplessness. Animal research has shown that psychological stress increases CRH content in the amygdala [260,261]. Two major receptor types (each with several subtypes), CRH-R1 and R2, mediate CRH neurotransmission. The two types of CRH receptors appear to exert opposing effects, with CRH-R1 mediating anxiogenic

Table 2
Potential therapeutic agents for PTSD

Class	Agent	Mechanism of action	Rationale	Potential clinical effect
LHPA axis components	Antalarmin	CRH-1 receptor antagonist	Impede consolidation. Decrease 5HT activation and improve learned helplessness. Reduce sensitixation	Diminish intensity of conditioned response. Diminish arousal
	ASV-30	CRH-2 receptor antagonist	Prevent learned helplessness	Lessen avoidance, improve interpersonal behavior
	Spironolactone	MR antagonist	Impede consolidation/reconsolidation. Reduce sensitization	Reduce intensity of conditioned responses. Reduce non-specific arousal responses
	Mifepristone (RU-486)	GR antagonist	Impede consolidation/reconsolidation	Reduce intensity of conditioned responses
	SSR149415	AVP-1b receptor antagonism. Reduced HPA axis drive	Impede consolidation/reconsolidation Oppose learned helplessness. Decrease CRH effect	Anxiolysis; Reduce avoidance, enhance coping and improve mood
	DHEA	Modulate GABA-A receptor; Reduce cortisol/DHEA ratio; Excitotoxicity neuroprotection	Attenuates contextual fear conditioning. Alleviates 'learned helplessness'	Reduce environmentally incongruent conditioned fear responses. Improve mood and goal directed activity
Catecholaminergic agents	Propranolol	b-adrenergic anatagonist	Obstruct consolidation/reconsolidation. Inhibit recall. Reduce anxiety	Reduce intensity of cue and context conditioned responses. Decrease non-specific arousal responses
	Prazocin	Alpha adrenergic antagonist	Block arousal, inhibit sensitization, obstruct learned helplessness	Reduce anxiety, improve sleep/nightmare effect
Glutamatergic agents	LY354740 (or similar)	Group II glutamate 2/3 NMDA metabotropic agonist, reduces glutamatergic neurotransmission	Disrupts fear learning and conditioned response. Neuroprotective: Reduction in NMDA neurotoxicity, increases TGF levels	Lessen intrusive memories, reduce conditioned responses. Inhibit arousal
	Memantine	Low-affinity NMDA channel blocker	Delays contextual conditioning. Provides excitotoxicity neuroprotection	Reduces arousal and contextual conditioning responses
	Riluzole	Inhibits glutamate release. Blunts GABA-an inverse agonist	Modulation of LHPA axis response Excitotoxicity neuroprotection	Reduction of LHPA drive
	D-Cycloserine	NMDA partial agonist	Enhance extinction. Usage together with cognitive behavioral therapy	Reduced cue and context conditioned responses
Anticovulsantts	Lamotrigine	Blocks voltage-gated Na(+) channels and reduces glutamate release. Suppresses GABA(A) receptor synaptic transmission	Disrupts fear learning, fear potentiated startle. Anti kindling/sensitization	Improvement mostly in reexperiencing and avoidance/withdrawal symptoms
	Topiramate	Blocks state-dependent sodium channel. Potentiates GABA anxiolysis at non-BZD site; Blocks amygdala kainate/AMPA receptors	Disrupt associative learning, Delay sensitization/kindling	Reduce intrusive memories and arousal symptoms (improves sleep)
	Valproic acid	Blocks degeneration of GABA transaminase; Block voltage-gated calcium channels. Suppresses protein kinase C	Delay sensitization/kindling/arousal	Reduction in intrusive memories and hyperarousal symptoms. Improved mood and activity
	Pregabalin, gabapentin	GABA signal modulators, via GABA transporter 1 (GAT1)	Delay sensitization/kindling/arousal	Reduce autonomic hyperarousal symptoms (improve sleep)

Serotonergic agents	Buspirone	5HT1-A partial agonist	Prevent sequelae of inescapable stress	Reduced intrusions. Improved mood, increase in energy
	Mirtazapine	Adrenergic: alpha 1 agonist, alpha 2 antagonist. Serotonin: 5HT1A agonist, 5HT2A, 5HT2C, 5HT3 antagonist	Prevent inescapable stress sequelae. Activate serotonergic system, directly and via NE	Improve mood, increase energy, lessen intrusion
	Nefazodone	5HT2-A antagonist. Partial 5HT and noradrenaline reuptake inhibitor	Prevent sequelae of inescapable stress, improve coping and mood, reduce anxiety	Improvement in intrusion and hyperarousal symptoms

CRH: corticotrpin releasing hormone; 5HT: serotonin; MR: mineralocorticoid receptor; GR: glucocorticoid receptor; AVP: arginine vasopressin; HPA: hypothalamus-pituitary-adrenocortical; GABA: gamma-aminobutyric acid; DHEA: dehyroepiandrosterone; NMDA: *N*-methyl-D-aspartate; TGF: transforming growth factor; LHPA: limbic- hypothalamus-pituitary-adrenocortical; BZD: benzodiazepine; AMPA: alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate; NE: Norepinephrine.

and depressogenic actions that are opposed by the anxiolytic properties of CRH-R2 [262]. CRH-R1 antagonists (antalarmin) prevented both establishment of fear and expression of already established fear in rats [263]. The same antagonist prevented expression of stress behaviors in rhesus monkeys [264]. Interestingly, the CRH-R1 antagonist induces only small decreases in levels of adrenocorticotropin (ACTH), cortisol, epinephrine and norepinephine in animals [265]. The activation of CRH receptors within the caudal dorsal raphe nucleus (DRN) during inescapable stress has been shown critical for the development of subsequent behavioral changes (i.e. learned helplessness). Intra-DRN administration of CRH-R2 antagonist dose-dependently blocked inescapable stress-induced behavioral changes, while the CRH-R1 antagonist, administered in the same manner, did not [266]. Moreover, the highly selective CRH-R2 agonist urocortin II caused inescapable stress-like behavioral changes in the absence of external stress. In another study, administration of CRH-R2 antagonists consistently produced an anxiolytic effect on animals exposed to various types of stress [267]. Although the initial impression was that antagonism of CRH-R1 would be more beneficial in resisting stress effects, recent data make a convincing case for considering CRH-R2 antagonists as well.

Given CRH's extensive involvement in mediating stress response, serotonin's involvement in the model of inescapable stress and SSRI's positive effect in PTSD, a connection between the serotonergic and CRH systems could be expected. Recent data support this contention, suggesting a role for CRH-1 in mediating stress related increases and decreases in 5HT levels [154,268] as well as 5HT effects on HPA axis (ACTH and cortisol secretion, see [269]).

4.2. Glucocorticoid and mineralocorticoid antagonists

Cortisol binds with high affinity to MR and with moderate affinity to GR. Therefore, MR are continuously occupied throughout the day, exerting tonic inhibition upon HPA axis function, while GR appear to be primarily involved when cortisol levels are high (during stress and in the morning peak, in humans). By inhibiting CRH and ACTH secretion, these receptors regulate the release of cortisol.

Repeated inescapable fear stress in sheep (exposure to a dog) produced both increased levels of CRH in the amygdala and an exaggerated increase in CRH response to the presentation of a subsequent novel stress (a forelimb electric shock), an example of cross-sensitization [260]. Animals that had an escape route from the repeated dog stress did not show this CRH increase when faced with the novel stress. This is an example of how inescapable stress, in contrast with escapable stress, leads to cross sensitization. Administration of the glucocorticoid receptor antagonist mifepristone prior to exposure to the dog prevented

subsequent changes in CRH response [260]. Likewise, rats exposed to a single inescapable stressor session (15 min restraint) exhibited an anxiogenic-like behavior in the elevated plus-maze 24 h later. Intracerebroventricular infusion of either a selective GR antagonist or a selective MR antagonist to intact animals 15 min before restraint abolished the stress-induced anxiogenic effect [270]. Rats systemically injected with a GR antagonist either 1 h prior to conditioning or immediately after conditioning displayed less contextual fear conditioning than rats injected with a vehicle. No effect on auditory (cue) fear conditioning was observed [271]. These data suggest that different mechanisms are involved in context and cue conditioning, and that glucocorticoid activity contributes to processes of consolidation of emotional contextual memory. Another study showed that an interaction between levels of corticosterone and GRs modulates the extent to which memory for contextual fear conditioning is established and maintained [272].

Miferpristone (RU-486) has been administered to patients with depression, and the results have not been conclusive [273]. It may be more effective in psychotic depression [274]. As regards MR, a recent study by Young et al. [275] reports a difference in MR function between depressed patients and healthy controls. In PTSD, on the other hand, a preliminary study found no difference in MR activity between patients and healthy controls [276]. However, this study was limited as regards the time and duration of hormone level sampling and does not enable a reliable impression of MR function in PTSD. Spironolactone was effective in the treatment of pre-menstrual syndrome [277]. Further study into the role of MR and GR in PTSD pathophysiology is required before their antagonists can be considered potential therapeutic agents for PTSD.

4.3. Arginine vasopressin

Corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) are the major secretagogues of the HPA/stress system. AVP, however, has been studied much less than CRH, and our knowledge of the functional activity and pharmacology of AVP and its receptors in the regulation of HPA activity rests largely on studies conducted in rodents. The sensitivity of CRH and AVP transcription to glucocorticoid feedback apparently differ, and AVP-stimulated ACTH secretion may be refractory to glucocorticoid feedback. Vasopressinergic regulation of the HPA axis may, therefore, be critical for sustaining corticotrope responsiveness in the presence of high circulating glucocorticoid levels during chronic stress. It has been proposed that CRH plays a predominantly permissive role in HPA regulation while AVP represents the dynamic mediator of ACTH [278]. Extrahypothalamic AVP-containing neurons have also been characterized, notably in the medial amygdala, that innervate limbic structures such as the lateral septum and the ventral hippocampus. Like CRH, AVP also acts as a neurotransmitter, exerting its action by binding to specific G protein-coupled receptors of two types, V_{1a} and V_{1b}.

AVP has been implicated in learning and memory processes, pain sensitivity, synchronization of biological rhythms and the timing and quality of REM sleep. In PTSD, a nootropic effect of AVP was demonstrated by the enhanced autonomic nervous system response to personal combat imagery, PTSD indicating the facilitation of memory retrieval and conditioned fear response [279]. Accordingly, AVP V_1 antagonists have exhibited significant anxioloytic and antidepressive effect in various animal models of anxiety, and were particularly effective in models of traumatic stress exposure and inescapable stress conditions (see Ref. [280] for concise review and series of experiments).

In another AVP related human PTSD study available in the literature [281], increased serum prolyl endopeptidase (PEP, an AVP degradating enzyme) activity was found in PTSD, suggesting lower AVP levels in this disorder, that may lead to decreased HPA axis activity. The possibility of low AVP levels in PTSD is of particular interest given the discrepant findings of increased CSF-CRH levels and normal-low cortisol reported for this disorder. If ACTH and cortisol secretion are dependent upon synergistic activity of both AVP and CRH, low levels of AVP may inhibit cortisol secretion despite increased levels of CRH.

4.4. Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) are the major androgens secreted by the human adrenal glands [282]. DHEA was the first steroid hormone whose capacity to be synthesized within the brain was determined [283]. It is apparently also synthesized within glial cells, [284] and is termed a ‘neurosteroid’ [285]. Neurosteroid brain levels increase rapidly in response to stress, and have been postulated to counteract the negative effects of acute stress and return the organism toward homeostatsis [286]. DHEA is protective against excitatory amino acid and glucocorticoid induced neurotoxic hippocampal damage [287,288]. It attenuated contextual conditioned fear response in rats [289]. Serum concentrations of DHEAS in shocked, fear conditioned mice, were significantly lower than in non-shocked mice. DHEA alleviated behavioral despair in high-anxiety rats [290] and reduced the immobility time in mice submitted to the forced swimming test.

In healthy human subjects exposed to severe acute stress, DHEAS levels were significantly lower in subjects exhibiting more psychological symptoms of dissociation. Stress induced increase in DHEA was significantly greater in subjects who exhibited fewer symptoms of dissociation as well as in subjects with superior

performance under stress [291]. Likewise, stress induced increases in DHEA levels were found in healthy parachuters assessed right before and after their first jump [292]. In light of these findings from animal and human research, DHEA could be considered a potential anti-stress agent, and its levels in PTSD would be expected to be reduced. However, findings are not consistent. Three studies that similarly examined male combat veterans with chronic PTSD found reduced, [293] unchanged [294] and increased [182] DHEA levels compared to healthy controls. A recent study of stressed refugees, some of whom have PTSD, found that DHEAS levels correlated significantly with changes in self-rated symptoms of PTSD [295] and that DHEAS changed in opposite directions in PTSD and non-PTSD subjects [296] *was observed after treatment with DHEA*. Although results are not consistent, an association between DHEA and the emotional response to stress appears likely.

No treatment studies with DHEA have been performed in PTSD. As regards other disorders, moderate improvement in patients with major depression [297,298] and dysthymia [299]. In light of its responsivity to acute stress and neuroprotective capacity, a treatment trial with DHEA in acute stress disorder may be warranted.

4.5. Catecholaminergic agents

A high level of peritraumatic anxiety, reflected by elevated heart rate in the emergency room, was a risk factor for developing PTSD in most [300,301] but not all [302] studies performed to date. Increased anxiety is indicative of augmented catecholamine release. Catecholamines enhance emotional memory consolidation and hyperarousal/sensitization in PTSD. Propranolol, a beta-adrenergic antagonist, is currently administered for migraine, impulse dyscontrol syndromes, akathesia and peripheral manifestations of anxiety. Favorable preliminary results have been reported following administration of propranolol in acute, chronic and reemergent PTSD [257,258,303–305].

Administration of the alpha-1 adrenergic antagonist prazosin to rats abolished NMDA mediated fear learning [239]. A series of studies examining the effect of prazosin in patients with PTSD reports favorable results in reduction of PTSD symptoms, particularly an improvement in sleep and decrease in nightmares [306–310]. Similarly, preliminary studies evaluating the efficacy of the alpha-2 adrenergic (and 5HT2A) antagonist mirtazapine have also described favorable effects of this agent [311–315], again with a notable effect upon quality of sleep and reduction of nightmares (in this case related more to 5HT2A and possibly histaminergic blockade [316]).

It is suggested that the treatment studies with propranolol will first be directed towards patients with acute stress disorder or acute PTSD, in whom conditioning may still be ongoing and emotional memory consolidation may still be in progress. As described above, even fully consolidated memories become unstable upon reactivation [30] and require repeat consolidation. Propranolol blocks rereconsolidation as well or even better than it does initial consolidation [32]. Since prolonged exposure (PE) psychotherapy is based upon reactivation of traumatic memories, it may be worthwhile to combine this agent with psychotherapy, administering propranolol at the end of each session. Still, since the effect of PE is presumably mediated by extinction like process, propranolol's beneficial effect in diminishing reconsolidation of the traumatic memories may also impair extinction.

Evaluation of the efficacy of prazosin and mirtazapine should be continued with patients suffering from the chronic form of the disorder, particularly those exhibiting high levels of anxiety, sleep disturbance and nightmares. Although each agent interacts in a unique manner with the catecholaminergic system, all appear to possess similar hypnotic and anti-sensitization effects that may be particularly relevant to the hyperarousal cluster of symptoms.

4.6. Glutamatergic agents

Although glutamate is the major excitatory neurotransmitter in the central nervous system, there is little direct clinical evidence in PTSD for altered glutamate function. The potential use of glutamatergic agents in PTSD is, therefore, inferred from the abundance and diversity of glutamatergic activity in preclinical research. Stress activates widespread cortical and limbic glutamatergic systems [317]. Immediate increase in glutamate efflux in prefrontal cortex and hippocampus were observed after induction of acute stress [318]. NMDA receptors may mediate lasting increases in anxiety-like behavior produced by the stress of predator exposure [239]. Ionotropic and metabotropic glutamate receptors, mostly located in the amygdala, are involved in both learning and expressing fear responses [94]. Given glutamate's numerous, and sometimes conflicting roles in modulating stress response, choice of a glutamatergic therapeutic agent is not simple.

Partial NMDA agonists (i.e. D-Cycloserine) may facilitate extinction [55]. These agents could be particularly useful and synergistic with cognitive behavioral psychotherapy. However, due to potential enhancement of glutamatergic neurotransmission and facilitation of all glutamate related learning (i.e. both acquisition and extinction of the fear response), we suggest that such agents be used carefully, perhaps limiting their use to treatment of subjects with chronic PTSD in conjunction with cognitive behavioral psychotherapy.

Metabotropic glutamate receptors function to modulate neuronal excitation and plasticity via pre-synaptic, post-synaptic and glial mechanisms [319]. Agonists for group II mGlu receptors, such as LY354740, have been shown to suppress enhanced glutamatergic excitations in brain synapses involved in the expression of fear/anxiety in

animals and humans [96]. A recent study that investigated the anxiolytic effects of LY354740 in humans using the fear-potentiated startle reflex methodology found that this compound significantly reduced the increase in startle magnitude during shock anticipation, without being sedative [320].

Riluzole is a glutamate antagonist used for treatment of amyotrophic lateral sclerosis (ALS) that inhibits glutamate release from presynaptic terminals. An early preclinical study suggests that riluzole blunts the anxiogenic properties of the GABA inverse agonist β-carboline, FG 7142 [321]. Recent clinical human studies suggest that it may have efficacy in downmodulating the HPA axis response to stress [322]. Since clinical experience in treatment of PTSD with Riluzole *is lacking*, its efficacy should first be tested in small, open label studies.

4.7. Anticonvulsants

Lamotrigine is an anticonvulsant that stabilizes neuronal membranes and attenuates cortical glutamate release via inhibition of sodium, calcium and potassium channels [323]. It was superior to placebo in a preliminary treatment trial of PTSD, with improvement mostly in reexperiencing and avoidance/numbing symptoms [324]. In addition, single dose administration of lamotrigine 2 hours before administration of ketamine significantly reduced the latter's dissociative and cognitive effects [325]. Since dissociative symptoms are particularly prominent in acute stress disorder, and in light of glutamate's enhancement of fear conditioning, clinical trials of lamotrigine in the acute stages of the disorder are warranted.

Another anticonvulsant, topiramate, inhibits amygdala AMPA/kainate receptors, stimulates GABA(A) neurotransmission [326] and blocks voltage-gated Na^{+}channels [327]. A recent animal study reports that topiramate attenuated exaggerated acoustic startle in an animal model of PTSD [328]. Topiramate was also found to reduce nightmares and flashbacks in an open-label study of 35 chronic PTSD patients [329]. Considering topiramate's favorable results with chronic PTSD, and since the acoustic startle reflex in PTSD appears to be an acquired response, not present in the acute aftermath of trauma [201,330], clinical trials with this agent should focus on patients with chronic PTSD.

Valproate (valproic acid) has become the most widely prescribed antiepileptic drug worldwide. Its pharmacological effects are mediated by a variety of mechanisms, including increased GABAergic transmission, reduced release of excitatory amino acids, inhibition of voltage-gated sodium channels and modulation of dopaminergic and serotoninergic transmission [331]. Several positive preliminary trials of valproate administration in PTSD have been reported in the past decade [332–336], although a definitive controlled study of the efficacy of this agent in PTSD is yet to be performed.

The BZD-GABA receptor complex is made up of five subunits, with the anxiolytic effects of BZD receptor agonists apparently mediated by the $GABA_A$ receptor $alpha_2$ subunit, which is largely expressed in the limbic system, but not in the $alpha_1$ subunit, which is implicated in mediating the sedative, amnestic, and anticonvulsive effects of BZDs [340,341] or the $alpha_3$ subunit, which is predominantly expressed in the reticular activating system [341]. Neuroimaging studies in patients with PTSD and panic disorders have revealed reduced cortical and subcortical benzodiazepine receptor binding in patients with PTSD, and panic disorder [183,342,343]. The findings could be related to a down-regulation of benzodiazepine receptor binding following exposure to stress, changes in receptor affinity or changes in an endogenous benzodiazepine ligand (the existence of which is controversial). Although BZD provide rapid and effective relief of anxiety and panic symptoms [344,345], in PTSD their efficacy is less potent (see above). Thus, the BZD antagonist flumazenil evokes panic symptoms in patients with panic disorder [346], but does not bring about such symptoms in PTSD [347,348]. This suggests that in spite of the phenomenological similarity between PTSD and panic disorder, the pathophysiology may substantially differ.

An interaction between serotonergic and GABA systems has recently been demonstrated in rodents. 5HT1A receptor knockout mice show BZD resistant anxiety, thought to reflect changes in GABAA receptor complex, particularly in the amygdala and hippocampus [349]. This supports the common practice of combining SSRI and benzodiazepines in the treatment of anxiety disorders. An interaction between the GABA/BZD system, stress and HPA axis is demonstrated by the finding that stress-induced increase in benzodiazepine receptors [350] is blocked by adrenalectomy and restored by corticosterone replacement, after both acute and chronic stress [351]. Additional support for the link between HPA and BZD receptors is drawn from the complex changes in the mRNA levels of multiple GABA(A) receptor subunits induced by 10 days of corticosterone administration [352,353].

As mentioned above, benzodiazepines have not been proven effective in ameliorating the core symptoms of PTSD [256,337]. This may be partly attributed to the role of GABA agonists/antagonists in extinction [95], as described above. McGaugh et al. [338] have shown in a preclinical study that the GABA antagonist picrotoxin enhances extinction if administered shortly after training. Along these lines, and similar to the NMDA agonist D-cycloserine mentioned above, administration of BZD antagonists in conjunction with extinction-like psychotherapies might prove synergistic.

Newer anti epileptic agents interact with GABAergic neurotransmission in a different manner [339], and thus offer renewed hope as potential threapeutic agents in anxiety disorders. The anticonvulsants pregabalin and gabapentin exert most of their brain action by interacting

with the BZD/GABA receptor complex. Their main site of action appears to be on the alpha(2)delta subunit of voltage-dependent calcium channels. Preliminary animal and human studies show beneficial effects in generalized anxiety disorder, social phobia and panic disorder, as well as sleep-modulating properties [339,354,355]. Promising results have also been reported for PTSD [356–359], although additional research is clearly warranted.

4.8. Serotonergic agents

The diversity of serotonin receptors and their broad distribution in the brain does not allow for a definition of 'serotonin effect' as regards mood and anxiety disorders, including PTSD. On the one hand, preclinical models of anxiety often correlate 5-HT function with aversive behavior, and show that drugs that reduce serotonergic function decrease fearful behaviors and demonstrate anxiolytic effects (reviewed in [238]). On the other hand serotonin prevents/ameliorates expression of learned helplessness after exposureto of inescapable stress [129]. This protectivity is conferred largely through post-synaptic 5HT1A receptors [140], and is in keeping with the findings of Gross et al. [108] that forebrain post-synaptic 5HT1A receptors, not the presynaptic receptors, are most important in modulating anxious behavior in rodents. Furthermore, the primate literature suggests that lowering 5-HT increases aggression, whereas increasing 5-HT decreases aggression and increases positive, affiliative behaviors and is associated with increased dominance in males [360]. Serotonergic input to key structures in the fear pathway (amygdala, locus ceruleus, periaqueductal gray) is considered inhibitory.

SSRIs are approved for treatment of most anxiety disorders, including PTSD and depression, although their mechanism of action is not fully understood. These agents will not be discussed here. The 5HT1A receptor subtype has been studied in humans with anxiety disorders. Full 5HT1A receptor agonists have been shown to worsen anxiety in panic disorder patients [361], while partial agonists have been shown to be ineffective in the treatment of panic disorder [362] but more effective in treatment of patients with generalized anxiety disorder. Clinical trials have demonstrated that 5HT2A/2C receptor antagonists, such as ritanserin and mianserin, are anxiolytic [106]. A summary of six open label studies of nefazadone administration in PTSD provided encouraging information of the efficacy this agent [363]. Therefore, 5HT1A partial agonists (buspirone) and 5HT2A receptor antagonists (mirtazapine, nefazadone) may serve to alleviate the arousal and anxiety symptoms continuously present in PTSD. Once anxiety symptoms are improved, the threshold for reexperiencing traumatic memories may also increase, lowering the frequency of this part of PTSDs symptomatology.

5. Concluding remarks

PTSD comprises a combination of interrelated neurobiological mechanisms, tightly linked and serving to augment the pathological response to stress. The therapeutic agents presented above each target a certain part these mechanisms. Intervention at a certain point in this complex may serve to gradually disentangle the complete symptom structure. For example, an intervention aimed at improving the learned helplessness condition could curb enhanced fear conditioning, enhance escape learning and coping skills, improve a person's mood and altogether abolish the 'inescapable' quality of the subjective experience of stress. Once this is achieved, recurrent aversive stimuli would no longer propagate fear conditioning and loose their pervasive quality. Patients would be able to withstand and handle emotional stimuli, putting an end to the harmful process of cross-sensitization and generalization, gradually expanding 'safe' territory and limiting the effect of aversive stimuli, until quality of life is restored.

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